REMARKS

Claims 23, 24, 26-28, and 40 are pending in the present application.

At the outset, Applicants wish to thank Examiner Zucker for the helpful and courteous discussions with their undersigned Representative on July 21, 2004 and October 26, 2004. During these discussions, various amendments to address the rejections over the art of record were discussed. The content of this discussion is believed to be reflected in the present response. Reconsideration of the remaining claims is requested in view of the following.

Present Claims 23 and 26 relate to crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester produced by:

(1) subjecting N-L-α-aspartyl-L-phenylalanine 1-methyl ester and 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or a derivative thereof to reductive alkylation in a solvent to obtain N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester; and

(2) crystallizing said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester,

wherein said reductive alkylation comprises catalytic hydrogenation,

wherein said derivative thereof is selected from the group consisting of

3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)-2-propenylaldehyde, and acetals derived therefrom, and

wherein said crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester exhibits X-ray diffraction peaks at 2θ diffraction angles of 5.55°, 12.25°, 18.5°, 21.1° and 22.45° with CuKα rays.

Present Claims 27 and 28 relate to certain sweetening agents which contain such crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

Claim 24 relates to a crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester exhibits X-ray diffraction peaks at 2θ diffraction angles of 5.55°, 12.25°, 18.5°, 21.1° and 22.45° with CuKα rays.

The cited references contain no disclosure or suggestion the claimed crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester polymorph. Moreover, these references contain no teaching that would instill a reasonable expectation of success for the presently claimed methods into one of skill in the art. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claim 24 under 35 U.S.C. §102(b) over Nofre et al (US 5,480,668) is traversed.

The Examiner has once again reinstated the inherency rejection of the claimed polymorph of Claim 24, despite withdrawing the same in the face of the Atwood Declaration submitted on September 25, 2003. No explanation is given for this rejection other than:

> "Nofre discloses (Column 8, Table 1, entries 18 and 19) the compound N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Nofre further discloses (Column 7, lines 24-51) a process for its synthesis and crystallization. The X-ray diffraction pattern of a crystalline compound is an inherent property of that compound." (Office Action mailed June 3, 2004, page 2)

Applicants traverse this rejection one many grounds. First, Applicants direct the Examiner's attention to MPEP §2112, which states:

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)

The Examiner has clearly failed to provide any reasonable basis in fact and/or technical reasoning to support a determination of inherency. In fact, all the Examiner has done is simply stated his conclusion – "X-ray diffraction pattern of a crystalline compound is an inherent property of that compound." However, no support is offered for this conclusion. As such, the Examiner has failed to make out a proper inherency case and, thus, the Examiner has failed to show how Nofre et al would anticipate the claimed invention.

The next error by the Examiner is in the conclusion/assertion that the "X-ray diffraction pattern of a crystalline compound is an inherent property of *that compound.*" (emphasis added) The Examiner is reminded that the X-ray diffraction pattern of a crystalline compound is not a direct measure of the compound itself, but rather is a measure of the manner in which the molecules relate to each other in the crystalline state.

The assertion by the Examiner would only have merit if every known compound were to have one and only one crystalline form and, therefore, by knowing the structure of the compound the specific interaction between the molecules in the crystalline state could be immediately envisioned. However, this is not the case and is overtly contradictory to decades worth of research in organic chemistry and small molecule crystallography.

The Examiner is reminded of the comments on the state of the art as it relates to polymorphism (i.e., two or more different crystalline forms for the same compound) provided

by Prof. Atwood in the Declaration under 37 C.F.R. §1.132 filed on September 25, 2003. For the Examiner's convenience paragraphs 10-13 are reproduced below:

> Many organic compounds crystallize in more than one form. That is to say, one given organic compound may crystallize in two or more different forms. These forms are not different in the way in which the atoms of the molecule are connected, but rather in the manner in which the molecules relate to each other in the crystalline state. This behavior is referred to as polymorphism. In 1965, McCrone defined a polymorph as "a solid crystalline phase of a given compound resulting from the possiblility of at least two different arrangements of the molecules of that compound in the solid state" (W. C. McCrone in *Physics and Chemistry of the Organic Solid State*, Vol. 2, (Eds.: D. Fox, M. M. Labes, and A Weissberger), pp. 725-67, Wiley Interscience, New York, 1965).
>
> Polymorphs may have very different physical properties such as melting point, dissolution rate, solubility, particle size, and hygroscopicity. One polymorph may be much more useful for a given purpose than is another polymorph, even though, chemically, the molecules are the same.
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> Polymorphs were first discovered by chance. Indeed, even with the substantial effort now being brought to bear to the polymorphism issue, there is no way to predict the existence of polymophism for a given compound, regardless of the information available about the manner in which the atoms are bonded together in the molecule. The American Chemical Society held a so-called "ProSpectives" course in polymorphism last February, and the second such course is scheduled for February 2004. The advertisement for this 2004 course is given in Exhibit B.
>
> While it is not possible to predict polymorphism, once polymorphs have been discovered, it is necessary to describe the methods and conditions of crystallzation which will afford reproducibility. In my opinion, it is not sufficient to simply state that a compound is crystallized from a given solvent. Polymorphs may be obtained even from the same solvent under different crystallization conditions. Therefore, the method by which a particular polymorph may reproducibly be obtained is as novel as the polymorph itself.

In view of the foregoing, Applicants submit that it has been clearly established in the art that the mere knowledge of the existence of a compound and its assigned structure is insufficient to predict whether one crystal form exists or whether multiple polymorphs exist. Further, in view of Prof. Atwood's comments, it is apparent that a general assertion of synthesis and crystallization of a compound in the abstract sense (e.g., Nofre et al) clearly fails to put a single polymorph in the hands of the artisan. Even more apparent from Prof.

Atwood's comments is that the X-ray diffraction pattern is related to the crystalline form (i.e., polymorph) and not to the compound itself.

Not only has the Examiner failed to provide any basis in fact or technical reasoning to support his inherency position (MPEP 2112), Applicants note that the Examiner has even failed to make a *prima facie* case of obviousness. When an Examiner maintains that there is an implicit teaching or suggestion in the prior art, "the Examiner should indicate where (page and line or figure) such a teaching or suggestion appears in the prior art." (*Ex parte* Jones, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001). However, as stated above, the Examiner has failed to provide a reason, explanation, or specific citation to support his statements set forth in the Office Action mailed June 3, 2004, page 2.

Further, MPEP §2142 states: "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation... to modify the reference... Second, there must be a reasonable expectation of success. Finally, the prior art reference... must teach or suggest all the claim limitations." In this case, not only has the Examiner failed to support an inherency rejection, the Examiner has also failed to provide any explanation of how the art would meet the aforementioned criteria to support even a *prima facie* case of obviousness.

Further evidence of (a) the fact that Nofre et al do not inherently disclose the claimed crystalline compound and (b) that the claimed crystalline compound would not be obvious in view of Nofre et al (even if combined with secondary references, infra), Applicants **submit herewith** an executed Declaration under 37 C.F.R. §1.132.

In paragraph 6 of the enclosed Declaration under 37 C.F.R. §1.132, it is noted that "even if a general reductive alkylation method (column 7, lines 24-51) for synthesizing the

compounds shown in Table 1 (column 8), and recrystallization of the compound from an ethanol/water mixture or acetonitrile (column 7, lines 48-49) are applied to the compound of the present invention, the aforementioned crystalline compound cannot be obtained." It is further noted that "using the process disclosed in Nofre et al, relatively water-soluble reagents and by-products may be removed from the reaction product; however, lipid-soluble impurities appeared to be extremely difficult to remove from the reaction product. In this condition, the inventive compound cannot be recrystallized due to the residual presence of lipid-soluble impurities... only after additional purification procedures to those disclosed by Nofre e al were added could N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester be obtained as a crystal."

Applicants submit that the enclosed Declaration under 37 C.F.R. §1.132 clearly demonstrates that the process disclosed by Nofre et al fail to inherently produce a crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, which exhibits X-ray diffraction peaks at 2θ diffraction angles of 5.55°, 12.25°, 18.5°, 21.1° and 22.45° with CuKα rays as presently claimed. In view of the foregoing, Nofre et al fail to anticipate and/or render the present invention obvious.

Applicants request withdrawal of this ground of rejection.

The rejections of: (a) Claims 23 and 26 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,480,668 (Nofre et al) in view of U.S. Patent No. 5,510,508 (Claude et al); and (b) Claims 27 and 28 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,480,668 (Nofre et al) in view of U.S. Patent No. 5,510,508 (Claude et al), are obviated in part by amendment and traversed in part.

Applicants note that Claim 23 has been amended to specify that the crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester exhibits X-ray diffraction peaks at 2θ diffraction angles of 5.55°, 12.25°, 18.5°, 21.1° and 22.45° with CuKα rays[1]. For the reasons set forth above, and further evidenced by the Declaration under 37 C.F.R. §1.132 submitted herewith, Nofre et al fail to disclose or suggest the claimed crystalline form or provide any reasonable expectation of how the skilled artisan would obtain the same.

Claude et al is cited as disclosing a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame. However, Claude et al do not compensate for the deficiencies in the disclosure of Nofre et al, which are further illustrated in the attached Declaration under 37 C.F.R. §1.132. Specifically, the combined disclosures of Nofre et al and Claude et al fail to disclose or suggest the following regarding the claimed N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester having the specifically recited X-ray diffraction peaks.

For the foregoing reasons, Nofre et al and Claude et al fail to render obvious the present invention. As such, these grounds of rejection should be withdrawn.

1 The amendment herein in no way is to be construed as acquiescence to the Examiner's conclusions and assertions in maintaining the previous grounds of rejection. Applicants continue to disagree with these conclusions by the Examiner for the reasons already of record. Applicants retain the right to present the previously rejected claims in an ensuing continuation application without prejudice.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

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